ZSTK - FOXO1A CLOCKWISE HYSTERESIS

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1. A possible explanatory mechanism

In physics, hysteresis describes systems that do not directly follow the forces applied to them, but react slowly, or do not return completely to their original state. In graphical terms (see Figure 1), if the depending variable Y precedes the dependent variable X, it is said that the relation X-Y shows clockwise (**CW**) hysteresis (when Y lags the dependent variable X, it is said that the relation X-Y shows counter clockwise hysteresis). When considering controlled mechanical systems, like robot manipulators, **CW** hysteresis appears as an undesired phenomenon related with relative motion between surfaces; **CW** hysteresis is common in dynamical friction models (see for instance [3]). As far as dynamic enzyme models are concerned, **CW** hysteresis has been studied from the beginning of computer-based research of enzymatic reactions (see for instance the early work [1], which discusses **CW** hysteresis in a reversible enzymatical reaction based on Henri's original stoichiometric equation), but there is not available published information concerning this phenomenon in experimentally modified signaling pathways when applying drug targeting regulation. Considering the experimental results summarized in Figure 2, **CW** hysteresis can be observed in the Zstk-FOXO1a plane (Figure 2-(a)). Can this behavior be described in mathematical terms, with a mathematical model summarizing the basic characteristics of the related controlled system? Dynamical friction models seems to offer a useful tool for this purpose. Consider for instance the Dahl model, which describes ball bearing friction (*i.e.* the tangential reaction force between a body in motion on a surface), as described by:

$$\frac{dY}{dX} = \sigma \left(1 - \frac{Y - \frac{Y_{\max}+Y_{\min}}{2}}{\frac{Y_{\max}-Y_{\min}}{2}} \operatorname{Sign}(v) \right).$$

In this model Y denotes the friction force and X denotes the displacement of the body in motion. σ is the stiffness coefficient (which is related with the experimental fact that friction behavior can be interpreted in terms of contact between bristles located between the surfaces, see for instance [4]). Y_{MAX} and Y_{MIN} denote the maximal and the minimal values of the measured force Y. v denotes the velocity of relative displacement between the surfaces. It must be pointed out that this model of friction does not depend on time (what drives the system is the sign of the relative velocity between the surfaces, *i.e.* $\operatorname{Sign}(v)$). This model shows the behavior shown in Figure 3 (with $Y_{MAX} = 0.8$, $Y_{MIN} = 0.3$, and $\sigma = 0.1$). As can be see, the models captures in qualitative terms the observed behavior shown in Figure 2-(a), with the concentration of $Zstk$ playing the role of the displacement X, and the concentration of nuclear FOXO1a playing the role of the friction force Y. The

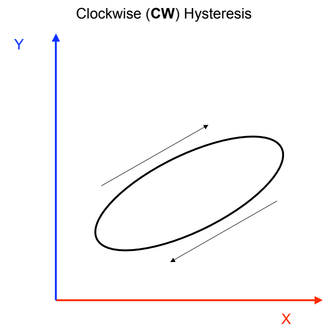

FIGURE 1. This figure shows in a simplified way the clockwise (**CW**) hysteresis behavior in the X - Y plane.

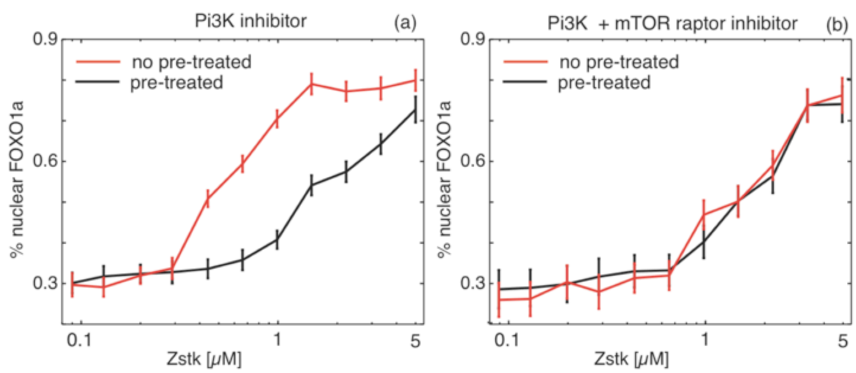

FIGURE 2. Experimentally observed hysteresis. (a)

key role of the sign of the velocity Sign (v) is played by the pre-treated and the no pre-treated play: Sign $(v) = 1$ for the no pre-treated case, and Sign $(v) = -1$ for the treated case (blue curve in Figure 3).

Since **CW** hysteresis is frequently associated to systems regulated by dominant negative feedback (see for instance [5]), the hysteretical behavior observed in the Zstk-FOXO1a plane (Figure 3-(a)) strongly suggest that the application of Zstk (inhibiting Pi3K) enhances the underlying negative feedback mechanism. When inhibiting mTOR raptor (see Figure 3/-(b)), the hysteresis is now not so evident, while suggest that the underlying negative feedback regulation is now not dominating the relation between Zstk and FOXO1a (since negative feedback frequently collaborate with cooperative (positive) a possible explanation of this behavior, is that the inhibition of mTOR raptor equilibrates collaboration between the underlying feedback regulators).

Hysteresis is common when confronting controlled systems driven by nonlinear dynamics. When modeling the reduced signaling pathway (non manipulated by the Zstk drug), the

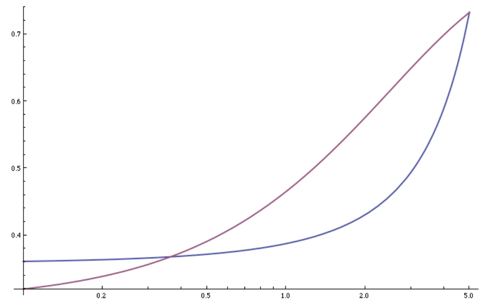

FIGURE 3. **CW** hysteresis in the dynamical friction model. This behavior is obtained fixing the parameters at the following values: $Y_{MAX} = 0.8$, $Y_{MIN} = 0.3$, and $\sigma = 0.1$. The red curve corresponds to $\mathrm{Sign}(v) = 1$, and the blue one corresponds to $\mathrm{Sign}(v) = -1$.

set of resulting differential equations is given by:

$$
\begin{aligned}
\dot{x}_1 &= -f_{MM}^{(K_1,a_1)}(x_6, x_1) - b_1 x_1 + b_1 u_1; \\
\dot{x}_2 &= f_{MM}^{(K_7,a_7)}(x_1, x_2) - b_2 x_2 - a_7 \tfrac{x_2}{K_7 + x_2} u_1 + b_2 u_2; \\
\dot{x}_3 &= f_{MM}^{(K_4,a_4)}(x_2, x_4) - f_{MM}^{(K_5,a_5)}(\overline{x_8}, x_3) - f_{MM}^{(K_2,a_2)}(x_1, x_3) + f_{MM}^{(K_5,a_5)}(\overline{x_8}, x_5) - f_{MM}^{(K_6,a_6)}(\overline{x_9}, x_3); \\
\dot{x}_4 &= -f_{MM}^{(K_4,a_4)}(x_2, x_4) + f_{MM}^{(K_3,a_3)}(\overline{x_8}, x_6) - f_{MM}^{(K_2,a_2)}(x_1, x_4) + f_{MM}^{(K_5,a_5)}(\overline{x_8}, x_3) + f_{MM}^{(K_6,a_6)}(\overline{x_9}, x_3); \\
\dot{x}_5 &= f_{MM}^{(K_4,a_4)}(x_2, x_6) + f_{MM}^{(K_2,a_2)}(x_1, x_3) - f_{MM}^{(K_5,a_5)}(\overline{x_8}, x_5) - f_{MM}^{(K_5,a_5)}(\overline{x_8}, x_5) - f_{MM}^{(K_6,a_6)}(\overline{x_9}, x_5) \\
\dot{x}_6 &= f_{MM}^{(K_2,a_2)}(x_1, x_4) - f_{MM}^{(K_3,a_3)}(\overline{x_8}, x_6) - f_{MM}^{(K_4,a_4)}(x_2, x_6) + f_{MM}^{(K_5,a_5)}(\overline{x_8}, x_5) + f_{MM}^{(K_6,a_6)}(\overline{x_9}, x_5),
\end{aligned}
$$

where $f_{MM}^{(K_i,a_i)}(x_i, x_j)$ stands for:

$$
f_{\mathrm{MM}}^{(K_i,a_i)}(x_i, x_j) := a_i x_i \frac{x_j}{K_i + x_j},
$$

and:

new name	old name	value or in. cond.	new name	old name	value or in. cond.
a_1	$\alpha_{\text{pAKT\_rictor}}$	10	K_1	$K_{\text{pAKT\_rictor}}$	10
a_2	$\alpha_{\text{rictor\_AKT}}$	20	K_2	$K_{\text{rictor\_AKT}}$	5.0
a_3	$\alpha_{\text{PP2A\_pAKT}}$	4	K_3	$K_{\text{PP2A\_pAKT}}$	0.1
a_4	$\alpha_{\text{PDK1p\_AKT}}$	20	K_4	$K_{\text{PDK1p\_AKT}}$	10.0
a_5	$\alpha_{\text{PP2A\_AKTp}}$	1	K_5	$K_{\text{PP2A\_AKTp}}$	0.1
a_6	$\alpha_{\text{PTEN\_AKTp}}$	1	K_6	$K_{\text{PTEN\_AKTp}}$	0.25
a_7	$\alpha_{\text{raptor\_PDK1p}}$	10	K_7	$K_{\text{raptor\_PDK1p}}$	10.0
x_1	$[rictor]$	0.0	$\overline{x_8}$	$[PP2A]$	150.0
x_2	[PDK1p]	50.0	$\overline{x_9}$	$[PTEN]$	200.0
x_3	$[AKTp]$	0.0	u_1	mTOR_total	100.0
x_4	$[AKT]$	100.0	u_2	PDK1_total	100.0
x_5	$[pAKTp]$	0.0	b_1	$\beta_{\text{raptor\_2\_rictor}}$	1.0
x_6	$[pAKT]$	0.0	b_2	$\beta_{\text{PDK1\_2\_PDK1p}}$	5.0

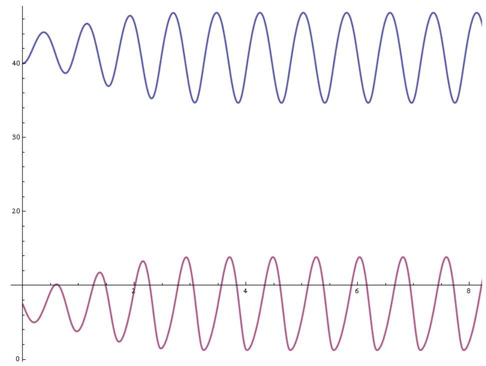

Figure 4. Sustained oscillation on the mathematical model of the reduced AKT signaling pathway. [rictor] is shown in blue and [pAKTp] is shown in red.

The numerical simulation of this system for the given parameters and initial conditions shows sustained oscillations, as can be see in Figure 4, where the time evolution of $[rictor]$ is shown in blue and $[pAKTp]$ is shown in red.

Since the oscillations displayed by the simulated dynamics are high-frequency ones, it would very hard to check if this property of the model corresponds to real sustained oscillations in the signaling pathway. Perhaps the oscillatory behavior is only a model artifact. However, the question deserves to be addressed. When considering the observed hysteretical behavior, it must be pointed out that the considered Dahl model assumes that between the surfaces in relative motion the contact is due to the presence of idealized bristles (considered as a sort of springs), and hysteresis is explained in terms of change of the elastic properties of the bristles. If the idealized bristles were oscillating, the hysteretical behavior would be attenuated. Thus, hysteresis would appear when applying Zstk because the sustained oscillations of the non manipulated signaling pathway are damped. Inhibition of mTOR raptor would reestablishes the underlying oscillations, reducing "friction". Which is to say, mTOR inhibition could be interpreted in mechanical terms as addition of oil between the surfaces in relative motion. It must be pointed out that friction compensation was attained for auto pilots in the 1940s, using a dither signal (that is a high frequency signal that is added to the control signal), and even now this technique is very common in mechanical systems involving relative motion between surfaces (see for instance [6] and the references therein).

As can be seen, the analogy between the observed hysteretical phenomenon in the Zstk-FOXO1a relation and mechanical friction offers some interesting possibilities. More specifically, concepts arising from applications concerning friction compensation on mechanical systems could find its way to the emerging field of control of signaling pathway (via targeting drug approaches).

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